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ORIGINAL ARTICLE

Prostate Cancer

Prostate health index can stratify patients with Prostate Imaging Reporting and Data System score 3 lesions on magnetic resonance imaging to reduce prostate biopsies

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We aim to evaluate prostate health index as an additional risk-stratification tool in patients with Prostate Imaging Reporting and Data System score 3 lesions on multiparametric magnetic resonance imaging. Men with biochemical or clinical suspicion of having prostate cancer who underwent multiparametric magnetic resonance imaging in two tertiary centers (Queen Mary Hospital and Princess Margaret Hospital, Hong Kong, China) between January 2017 and June 2022 were included. Ultrasound-magnetic resonance imaging fusion biopsies were performed after prostate health index testing. Those who only had Prostate Imaging Reporting and Data System score 3 lesions were further stratified into four prostate health index risk groups and the cancer detection rates were analyzed. Out of the 747 patients, 47.3% had Prostate Imaging Reporting and Data System score 3 lesions only. The detection rate of clinically significant prostate cancer in this group was 15.0%. The cancer detection rates of clinically significant prostate cancer had statistically significant differences: 5.3% in prostate health index <25.0, 7.4% in prostate health index 25.0–34.9, 17.9% in prostate health index 35.0–54.9, and 52.6% in prostate health index ≥55.0 ($P < 0.01$). Among the patients, 26.9% could have avoided a biopsy with a prostate health index <25.0, at the expense of a 5.3% risk of missing clinically significant prostate cancer. Prostate health index could be used as an additional risk stratification tool for patients with Prostate Imaging Reporting and Data System score 3 lesions. Biopsies could be avoided in patients with low prostate health index, with a small risk of missing clinically significant prostate cancer.

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Keywords: biopsy; fusion biopsy; magnetic resonance imaging; prostate cancer; prostate health index

INTRODUCTION

Multiparametric magnetic resonance imaging (mpMRI) has now become a recommended tool for evaluating men with clinical or biochemical suspicion of having prostate cancer.[1–3] This is based on evidence that mpMRI could reduce unnecessary biopsies for clinically insignificant cancers,[4,5] and that ultrasound-MRI fusion target and systematic biopsies have a higher cancer detection rate than systematic biopsies alone.[6]

The interpretation of prostate mpMRI has been standardized by the Prostate Imaging Reporting and Data System (PI-RADS).[7,8] Prostatic lesions on MRI are classified into five categories (PI-RADS scores 1–5) according to the estimated risk of csPCa. Prostate biopsies are recommended for PI-RADS score ≥3 lesions, but the optimal strategy for PI-RADS score 3 lesions is still under debate, as they are deemed to pose only an equivocal risk of harboring clinically significant prostate cancer (csPCa).[9–11]

The natural question is, therefore, how these PI-RADS score 3 lesion patients could be further risk-stratified to prioritize biopsies. There is currently a lack of evidence regarding the performance of prostate health index (PHI) in predicting csPCa in men who only have PI-RADS score 3 lesions. In this study, we analyzed whether PHI cutoff values for PI-RADS score 3 lesions could be generated to allow patients to delay or even omit biopsies at a minimal risk of missing csPCa. The aim is to provide practical tools for the urologist counseling PI-RADS score 3 lesion patients.

PATIENTS AND METHODS

Patients

Data were collected retrospectively from two tertiary referral centers in Hong Kong, China (Queen Mary Hospital and Princess Margaret Hospital) between January 2017 and June 2022. A total of 747 patients with prostate-specific antigen (PSA) ≥4.0 ng ml^{-1} or abnormal prostate digital rectal examination underwent mpMRI. Of these patients, 353 had PI-RADS score 3 lesions only on their mpMRI. These patients all received prebiopsy PHI testing, followed by transrectal or transperineal

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targeted and systematic biopsies (**Figure 1**). Written informed consent was obtained from all patients for mpMRI and biopsies. Patients who were contraindicated for MRI or had poor general condition precluding biopsies were excluded from the analysis. The PSA results were analyzed as part of the PHI testing panel. All PHI tests from the two hospitals were centralized and performed at the same laboratory (Pamela Youde Nethersole Eastern Hospital, Hong Kong, China). This study was approved by the Hospital Authority Clinical Research Ethics Review Board, Hong Kong, China (Approval No. IRB-2023-399).

MpMRI reporting

Seven hundred and forty-seven patients underwent contrast mpMRI with T2-weighted imaging (1.5 T with no endorectal coil) and diffusion-weighted imaging (DWI) with apparent diffusion coefficient in protocols specific for fusion biopsies were used. The mpMRIs were all reported by experienced radiologists with more than 6 years of experience. Lesions were classified according to the PI-RADS versions 2 and 2.1 standards.[7,8] Prostate volume was calculated using the ellipsoid formula. The patients' clinical information was available to the radiologists. A centralized uroradiology review mechanism was implemented for the participating institutions to re-evaluate the PI-RADS score 3 lesions before biopsies.

Biopsy protocol

Three hundred and fifty-three patients who only had PI-RADS score 3 lesions then received either transrectal or transperineal ultrasound-MRI fusion biopsy according to their preference. Regardless of the route, all biopsies were performed using the Artemis (Eigen Health, Grass Valley, CA, USA) semi-robotic system. An elastic fusion algorithm and ultrasound-MRI fusion program (ProFuse, Eigen Health, CA, USA) allowed for real-time fusion of the ultrasound and mpMRI images. Targeted biopsies (3 cores per target) followed by systematic biopsies were performed in all patients. The local protocol for systematic biopsies adopted the 12-core approach for the transrectal route and the modified Ginsburg protocol[12,13] for the transperineal route.

Statistical analyses

SPSS Statistics (IBM, Armonk, NY, USA) were used for the statistical analyses in this study. The commonly quoted PHI cutoffs proposed by Catalona *et al*.[14] (PHI <25.0, 25.0–34.9, 35.0–54.9, and ≥55.0) were used to distribute the patients into four groups according to their prebiopsy PHI results. The differences in cancer detection rates for all prostate cancer and csPCa (defined as biopsy results of International Society of Urological Pathology [ISUP] grade group ≥2) were then analyzed by cross-tabulation and χ^2 analysis. Analysis of variance (ANOVA) tests of the baseline characteristics between the four groups were performed to detect confounders. Receiver operating characteristic (ROC) curves for the detection of csPCa were generated for PHI, PHI density (PHID), PSA, and PSA density (PSAD). The area under the curve (AUC) of each ROC curve was then compared with paired-sample *t*-tests, using $P \leq 0.05$ as a cutoff for statistical significance.

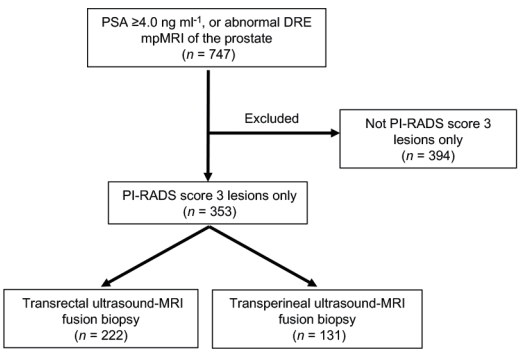

Figure 1: Flow diagram of the patient cohort. PSA: prostate-specific antigen; DRE: digital rectal examination; mpMRI: multiparametric magnetic resonance imaging; PI-RADS: Prostate Imaging Reporting and Data System.

RESULTS

Patients' characteristics

Patients' characteristics are shown in **Table 1**. Of the 747 patients, 353 (47.3%) had PI-RADS score 3 lesions only on mpMRI. The data from these 353 patients were further analyzed. The mean ± standard deviation (s.d.) age was 66.5 ± 6.0 years, mean ± s.d. PSA was 7.9 ± 3.7 ng ml^{-1}, and mean ± s.d. PHI was 36.2 ± 19.0. The cancer detection rate of csPCa, defined as a biopsy result of ISUP grade group ≥2, was 15.0% (53 out of the 353 patients). **Table 2** shows the differences in baseline characteristics between those who had csPCa and those who did not. The csPCa group had a higher mean PHI of 54.1, compared to 32.0 in those who did not ($P < 0.01$).

Subgroup analysis of patient characteristics from the two participating institutions was carried out to evaluate for heterogeneity. The baseline characteristics of the cohorts were found to be comparable, with only small differences in the patients' ages (mean age difference of 2) and prostate volumes. The differences in PSA densities between the two cohorts were statistically insignificant ($P = 0.06$; **Supplementary Table 1**).

Table 1: Patients' characteristics

Characteristic	*Value*
All patients (*n*)	747
Age (year), mean±s.d. (range)	66.5±6.0 (45–80)
PSA (ng ml^{-1}), mean±s.d. (range)	7.9±3.7 (1.7–30.9)
PHI, mean±s.d. (range)	36.2±19.0 (9.3–152.0)
Prostate volume (ml), mean±s.d. (range)	62.8±30.0 (14.0–191.0)
PSA density (ng ml^{-2}), mean±s.d. (range)	0.17±0.11 (0.03–0.80)
Patients with PI-RADS score 3 lesions only (*n*)	353
Biopsy results, *n*/total (%)	
No malignancy	254/353 (72.0)
ISUP=1	46/353 (13.0)
ISUP ≥2	53/353 (15.0)

s.d.: standard deviation; PHI: prostate health index; PSA: prostate-specific antigen; PI-RADS: Prostate Imaging Reporting and Data System; ISUP: International Society of Urological Pathology

Table 2: Characteristics of patients with Prostate Imaging Reporting and Data System score 3 lesions only according to biopsy results (*n*=353)

Characteristic	*Biopsy result*		
	ISUP ≥2 (n=53)	*Benign/ISUP=1 (n=300)*	*P*
Mean age (year)	67.1	66.7	0.07
Mean PSA (ng ml^{-1})	9.3	7.6	0.02
Mean PHI	54.1	32.0	<0.001
Mean prostate volume (ml)	42.3	61.1	<0.001
Mean PSA density (ng ml^{-2})	0.26	0.15	<0.001

PHI: prostate health index; PSA: prostate-specific antigen; PI-RADS: Prostate Imaging Reporting and Data System; ISUP: International Society of Urological Pathology

Stratification of PI-RADS score 3 lesion patients according to pre-biopsy PHI

The 353 patients who only had PI-RADS score 3 lesions were stratified into four categories according to their prebiopsy PHI. The cancer detection rates were then analyzed for each PHI category (**Table 3**). In those with PHI <25.0, the cancer detection rate of csPCa was 5.3% (5/95). This figure increased to 7.4% (8/108) in the next PHI category (PHI 25.0–34.9), followed by 17.9% (20/112) in the next category (PHI 35.0–54.9) and finally 52.6% (20/38) in the last category (PHI ≥55.0). The differences in cancer detection rates between the four PHI categories were statistically significant ($P < 0.01$). Using multivariable logistic regression, the relationship between PHI category and the odds of identifying csPCa was also proven to be statistically significant for PI-RADS score 3 lesions patients. Compared to those with PHI <25.0, the odds ratio of detecting csPCa was 1.45 ($P = 0.53$) in the PHI 25.0–34.9 group, 3.58 ($P = 0.02$) in the PHI 35.0–54.9 group and 16.72 ($P < 0.01$) in the PHI ≥55.0 group (**Supplementary Table 2**).

The cancer detection rates for csPCa between the transrectal and transperineal routes were 17.6% and 10.7%, respectively. The difference was not statistically significant ($P = 0.09$). When considering all PCa, the cancer detection rates were 29.7% and 25.2%, respectively, and the difference of which was also not statistically significant ($P = 0.39$; **Table 3**). This part of the analysis was performed to detect any differences between the two routes of biopsies, as the number of cores taken for systematic biopsies was different between them (12-core approach for the transrectal route and the modified Ginsburg protocol[12,13] for the transperineal route).

To exclude patient age and prostate size as confounders for the differences between the four PHI categories, ANOVA tests were performed, showing that there were no statistically significant differences ($P = 0.84$ and 0.09 for patient age and prostate size, respectively).

Performance of PHI versus other indices in PI-RADS score 3 lesion patients

The discriminative power of PHI was compared to that of PHID, PSAD, and PSA. ROC curves were generated for all four indices, as shown in **Figure 2**. The area under the curve was 0.758 for PHI ($P < 0.01$), 0.799 for PHID ($P = 0.15$), 0.734 for PSAD ($P = 0.56$), and 0.605 for PSA ($P < 0.01$). When comparing the AUC of PHI against that of the other three indices, only the AUC of PSA showed a statistically significant difference ($P < 0.01$).

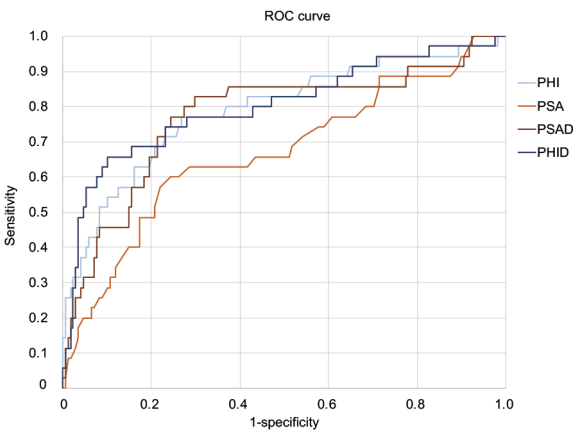

Figure 2: ROC curves of PHI, PHID, PSAD, and PSA for PI-RADS score 3 lesion patients. ROC: receiver operating characteristic; PHI: prostate health index; PSA: prostate-specific antigen; PI-RADS: Prostate Imaging Reporting and Data System; PSAD: prostate-specific antigen density; PHID: prostate health index density.

DISCUSSION

The use of mpMRI in the evaluation of men suspected to have prostate cancer has become increasingly important, as supported by the National Comprehensive Cancer Network (NCCN) and other major international guidelines.[1–3] Multiple landmark studies have demonstrated the advantages of mpMRI before biopsies for improving cancer detection rates.[4–6,15] Apart from mpMRI, PHI is another tool that has been gaining attention that aids decision-making for men at risk of having prostate cancer.[16] The large prospective study by Catalona *et al.*[14] has demonstrated that PHI outperforms total PSA and percentage-free PSA in the identification of prostate cancer. In this study, the utility of PHI in triaging men who only have PI-RADS score 3 lesions, which are deemed equivocal for csPCa,[9–11] was studied. We evaluated the prevalence of csPCa in different PHI ranges and also the performance of PHI compared to PSAD, PHID, and PSA alone.

A large portion of men (47.3%) who receive mpMRI was reported to have PI-RADS score 3 lesions only. Furthermore, only a small proportion of these men (15.0%) have csPCa, similar to the figure reported in the PROMIS trial.[4] Using a PHI cutoff of <25.0, 26.9% of biopsies could have been avoided at the cost of missing 5.3% (5/95) of csPCa. If a PHI cutoff of <35.0 was used instead, 57.5% of the biopsies could be avoided, at the cost of missing 6.4% (13/203) of csPCa. The balance between the risks of fusion biopsies and the risk of missing csPCa by delaying or omitting biopsies should be the part of the discussion between the urologists and the patients.

PHI performs differently when applied to patients who also have PI-RADS score 3 lesions. Previous studies on PHI without mpMRI in the Asian population showed that the cancer detection rate for csPCa with PHI <25.0 was only 1.0%.[17] Our results show that the cancer detection rate for csPCa is higher at PHI <25.0 if the patient also has a PI-RADS score 3 lesion. As expected, there is also an increasing trend in the probability of detecting csPCa in PI-RADS score 3 lesion patients as PHI increases, as shown in **Table 3**.

The ability of PHI in predicting csPCa in PI-RADS score 3 lesion patients was found to be comparable to that of PHID and PSAD. However, there are several advantages of using PHI over PSAD. First,

Table 3: Cancer detection rate by prostate health index category in patients with Prostate Imaging Reporting and Data System score 3 lesions

Patient	*Cancer detection rate of all prostate cancers (n=99)*	*Cancer detection rate of csPCa (ISUP grade group ≥2; n=53)*
PHI category		
<25.0, % (*n*/total)	16.8 (16/95)	5.3 (5/95)
25.0–34.9, % (*n*/total)	22.2 (24/108)	7.4 (8/108)
35.0–54.9, % (*n*/total)	26.8 (30/112)	17.9 (20/112)
≥55.0, % (*n*/total)	76.3 (29/38)	52.6 (20/38)
[a]*P*	<0.01	<0.01
Biopsy route		
Transrectal, % (*n*/total)	29.7 (66/222)	17.6 (39/222)
Transperineal, % (*n*/total)	25.2 (33/131)	10.7 (14/131)
[b]*P*	0.39	0.091

[a]The comparison of cancer detection rates between the above PHI categories; [b]The comparison of cancer detection rates between the two biopsy routes. PHI: prostate health index; csPCa: clinically significant prostate cancer; ISUP: International Society of Urological Pathology

PSAD may be subject to errors in the measurement of prostate size, as most radiologists estimate prostate volume with formula-based means.[18–20] Second, as PSAD is inherently a small number, stratification into groups would rely on differences at two or more decimal places, increasing the likelihood of errors. If a PSAD of 0.15 ng ml^{-2} was employed as a single cutoff[21,22] in PI-RADS score 3 lesion patients, there would be more heterogeneity than using the four PHI categories in this study. Using the results from this study, we could illustrate to a patient who only has PI-RADS score 3 lesions what his risk of missing csPCa from omitting a biopsy is based on his PHI result. Using a PHI of <25.0 as an example, the patient could expect the risk to be 5.3%. Conversely, for a patient who has a PHI of 30.0 (thus falling under the PHI category of 25.0–34.9), his chance of missing csPCa from omitting a biopsy would be 6.4% instead. More information could hence be gained from using the four PHI cutoffs than the single PSAD cutoff of 0.15 ng ml^{-2}. A recent study by Drevik *et al*.[23] with mainly Caucasian and African–American patients showed that using a PSAD cutoff of 0.15 ng ml^{-2}, 65% of patients with PI-RADS score 3 lesions could avoid a biopsy, with a 13.6% risk of missing csPCa. Although a much larger percentage of patients could avoid a biopsy, the 13.6% risk of missing csPCa may not be acceptable to some patients. From the public health or hospital policy point of view, the PHI cutoff categories also allow for more informed decision-making when managing entire cohorts of PI-RADS score 3 lesion patients. Policy-makers could estimate the total number of csPCa cases missed if patients under entire PHI cutoff groups were to omit biopsies. For example, 26.9% of biopsies could be avoided using a cutoff of <25.0, at the expense of missing 5.3% of csPCa. However, 57.5% of biopsies could be avoided if a cutoff of <35.0 was used instead, at the expense of missing 6.4% of csPCa.

This is a study that focuses on the performance of PHI in PI-RADS score 3 lesion patients receiving software fusion biopsy. The large sample size, with data pooled from two tertiary referral centers, is one of the strengths of this study. The reporting of the mpMRI was not restricted to any particular radiologist, but all reports received by the two tertiary referral centers were included. This allows our data set to represent the real-world situation, where urologists indeed receive mpMRI reports from many different radiologists. This also minimizes bias in the PI-RADS reporting from any one radiologist. However, the heterogeneity in radiologists and the potential for inter-observer variability could also be viewed as a limitation, especially as PI-RADS score 3 lesions are equivocal by nature.

There are some limitations in this study. First, the patients included did not all receive biopsies by the same route. Although all of them received targeted and systematic biopsy, some were biopsied transperineally and others transrectally. It may be argued that this could impact the yield of csPCa, as the number of cores taken during systematic biopsies was different between the transperineal and transrectal routes (12-core approach for the transrectal route and the modified Ginsburg protocol[12,13] for the transperineal route). However, when the differences in cancer detection rates between the two biopsy routes were analyzed separately and compared, the differences were statistically insignificant (**Table 3**). Second, the inclusion of patients from January 2017 to June 2022 allowed this study to enjoy a large sample size. However, PI-RADS version 2.1 was introduced in 2019 as an update to PI-RADS version 2. There is hence heterogeneity in the PI-RADS systems adopted in the MRI reporting. Future studies could focus only on scans reported with PI-RADS version 2.1 by omitting data before the introduction of this update.

The additional statistical analyses to evaluate for heterogeneity between the data from the two participating institutions showed that the baseline characteristics of the cohort were comparable. Larger cohorts should still be accrued for future studies to provide more accurate estimations of detection rates of csPCa in PI-RADS score 3 lesion patients as well as to increase statistical power.

In conclusion, PHI is a useful tool to stratify patients who only have PI-RADS score 3 lesions. Using a PHI cutoff of <25.0 as an example, 26.9% of biopsies could be delayed or avoided, with a 5.3% risk of missing csPCa. Clinicians should therefore incorporate the interpretation of PHI into their discussion with patients who only have PI-RADS score 3 lesions. A period of PHI monitoring instead of upfront biopsies could be an acceptable alternative after a thorough discussion with the patient. We follow these patients up in 6-month intervals if they have a PHI of <25.0 and opt to omit a biopsy. Future studies with longer follow-up periods and larger cohorts could help determine the optimal follow-up strategy for this group of patients.

AUTHOR CONTRIBUTIONS

JSLL, WKM, BSHH, CYN, CHI, ATLN, and YCL performed the fusion biopsies. JSLL, STTC, RN, and YZ performed the statistical analyses. JSLL, WKM, and BH conceptualized and designed the study and drafted the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

Supplementary Information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

REFERENCES

1 EAU Guidelines on Prostate Cancer. Arnhem: EAU Guidelines Office; 2022. Available from: https://uroweb.org/course/eau-guidelines-on-prostate-cancer. [Last accessed on 2023 Jan 16].
2 National Institute for Health and Care Excellence (NICE). Prostate Cancer: Diagnosis and Management: Guidance. London: National Institute for Health and Care Excellence (NICE); 2019. Available from: https://www.nice.org.uk/guidance/ng131/chapter/recommendations. [Last accessed on 2023 Jan 16].
3 Mason BR, Eastham JA, Davis BJ, Mynderse LA, Pugh TJ, *et al*. Current status of MRI and PET in the NCCN guidelines for prostate cancer. *J Natl Compr Canc Netw* 2019; 17: 506–13.
4 Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, *et al*. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *Lancet* 2017; 389: 815–22.
5 Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, *et al*. MRI-targeted or standard biopsy for prostate-cancer diagnosis. *N Engl J Med* 2018; 378: 1767–77.
6 Rouvière O, Puech P, Renard-Penna R, Claudon M, Roy C, *et al*. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-first): a prospective, multicentre, paired diagnostic study. *Lancet Oncol* 2018; 20: 100–9.
7 Weinreb JC, Barentsz JO, Choyke PL, Cornud F, Haider MA, *et al*. PI-RADS prostate imaging – reporting and data system: 2015, version 2. *Eur Urol* 2016; 69: 16–40.
8 Turkbey B, Rosenkrantz AB, Haider MA, Padhani AR, Villeirs G, *et al*. Prostate imaging reporting and data system version 2.1: 2019 update of prostate imaging reporting and data system version 2. *Eur Urol* 2019; 76: 340–51.
9 Schoots IG. MRI in early prostate cancer detection: how to manage indeterminate or equivocal PI-RADS 3 lesions? *Transl Androl Urol* 2018; 7: 70.
10 Scialpi M, Martorana E, Aisa MC, Rondoni V, D'Andrea A, *et al*. Score 3 prostate lesions: a gray zone for PI-RADS v2. *Turk J Urol* 2017; 43: 237.
11 Zhang Y, Zeng N, Zhang F, Huang Y, Tian Y. How to make clinical decisions to avoid unnecessary prostate screening in biopsy-naïve men with PI-RADs v2 score ≤3? *Int J Clin Oncol* 2019; 25: 175–86.
12 Hansen N, Patruno G, Wadhwa K, Gaziev G, Miano R, *et al*. Magnetic resonance and ultrasound image fusion supported transperineal prostate biopsy using the Ginsburg protocol: technique, learning points, and biopsy results. *Eur Urol* 2016; 70: 332–40.
13 Hansen NL, Barrett T, Lloyd T, Warren A, Samel C, *et al*. Optimising the number of cores for magnetic resonance imaging guided targeted and systematic transperineal prostate biopsy. *BJU Int* 2019; 125: 260–9.
14 Catalona WJ, Partin AW, Sanda MG, Wei JT, Klee GG, *et al*. A multicenter study of [-2]pro-prostate specific antigen combined with prostate specific antigen and free

prostate specific antigen for prostate cancer detection in the 2.0 to 10.0 ng/ml prostate specific antigen range. *J Urol* 2011; 185: 1650–5.
15 Ahdoot M, Wilbur AR, Reese SE, Lebastchi AH, Mehralivand S, *et al*. MRI-targeted, systematic, and combined biopsy for prostate cancer diagnosis. *N Engl J Med* 2020; 382: 917–28.
16 Loeb S, Shin SS, Broyles DL, Wei JT, Sanda M, *et al*. Prostate health index improves multivariable risk prediction of aggressive prostate cancer. *BJU Int* 2016; 120: 61–8.
17 Chiu PK, Ng CF, Semjonow A, Zhu Y, Vincendeau S, *et al*. A multicentre evaluation of the role of the prostate health index (PHI) in regions with differing prevalence of prostate cancer: adjustment of PHI reference ranges is needed for European and Asian settings. *Eur Urol* 2019; 75: 558–61.
18 Hamzaoui D, Montagne S, Granger B, Allera A, Ezziane M, *et al*. Prostate volume prediction on MRI: tools, accuracy and variability. *Eur Radiol* 2022; 32: 4931–41.
19 Snoj Z, Gill AB, Rundo L, Sushentsev N, Barrett T. Three-dimensional MRI evaluation of the effect of bladder volume on prostate translocation and distortion. *Radiol Oncol* 2020; 54: 48–56.
20 Wasserman NF, Niendorf E, Spilseth B. Measurement of prostate volume with MRI (a guide for the perplexed): biproximate method with analysis of precision and accuracy. *Sci Rep* 2020; 10: 575.
21 Schoots IG, Osses DF, Drost FH, Verbeek JF, Remmers S, *et al*. Reduction of MRI-targeted biopsies in men with low-risk prostate cancer on active surveillance by stratifying to PI-RADS and PSA-density, with different thresholds for significant disease. *Transl Androl Urol* 2018; 7: 132–44.
22 Nordström T, Akre O, Aly M, Grönberg H, Eklund M. Prostate-specific antigen (PSA) density in the diagnostic algorithm of prostate cancer. *Prostate Cancer Prostatic Dis* 2017; 21: 57–63.
23 Drevik J, Dalimov Z, Uzzo R, Danella J, Guzzo T, *et al*. Utility of PSA density in patients with PI-RADS 3 lesions across a large multi-institutional collaborative. *Urol Oncol* 2022; 40: 490.e1–6.

Supplementary Table 1: Comparison of patient characteristics between two centers (mean±standard deviation)

	QMH (n=293)	*PMH (n=60)*	*P*
Mean age (years)	66.0±6.0	68.0±6.1	0.024
Mean PSA (ng/ml)	7.8±3.5	8.4±4.9	0.260
Mean PHI	35.3±19.4	39.6±16.9	0.110
Mean prostate volume (ml)	56.2±29.8	67.5±31.6	0.010
Mean PSA density (ng/ml^2)	0.16±0.05	0.11±0.06	0.064

s.d.: standard deviation; QMH: Queen Mary Hospital; PMH: Princess Margaret Hospital; PSA: prostate-specific antigen; PHI: prostate health index

Supplementary Table 2: Multivariable logistic regression model on prostate health index category predicting prostate cancer risk among patients with PIRADS 3 lesions

PHI category Overall	*PCa*		*csPCa*	
	OR (95% CI)	*P*	*OR (95% CI)*	*P*
<25	1.00		1.00	
25–35	1.56 (0.76–3.24)	0.227	1.45 (0.46–4.64)	0.528
35–55	1.83 (0.89–3.76)	0.103	3.58 (1.26–10.20)	0.017
>55	15.73 (5.90–41.95)	<0.001	16.72 (5.30–52.74)	<0.001

PCa: prostate cancer; csPCa: clinically significant PCa; OR: odds ratio; CI: confidence interval; PHI: prostate health index